Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling

Macdonald, R Loch ; Higashida, Randall T ; Keller, Emanuela ; Mayer, Stephan A ; Molyneux, Andy ; Raabe, Andreas ; Vajkoczy, Peter ; Wanke, Isabel ; Bach, Doris ; Frey, Aline ; Nowbakht, Pegah ; Roux, Sébastien ; Kassell, Neal

Abstract: BACKGROUND AND PURPOSE: Clazosentan, an endothelin receptor antagonist, has been shown to reduce vasospasm after aneurysmal subarachnoid hemorrhage (aSAH). CONSCIOUS-3 assessed whether clazosentan reduced vasospasm-related morbidity and all-cause mortality postaSAH secured by endovascular coiling. METHODS: This double-blind, placebo-controlled, phase III trial randomized patients with aSAH secured by endovascular coiling to 14 days intravenous clazosentan (5 or 15 mg/h) or placebo. The primary composite end point (all-cause mortality; vasospasm-related new cerebral infarcts or delayed ischemic neurological deficits; rescue therapy for vasospasm) was evaluated 6 weeks postaSAH. The main secondary end point was dichotomized extended Glasgow Outcome Scale (week 12). RESULTS: CONSCIOUS-3 was halted prematurely following completion of CONSCIOUS-2; 577/1500 of planned patients (38%) were enrolled and 571 were treated (placebo, n=189; clazosentan 5 mg/h, n=194; clazosentan 15 mg/h, n=188). The primary end point occurred in 50/189 of placebo-treated patients (27%), compared with 47/194 patients (24%) treated with clazosentan 5 mg/h (odds ratio [OR], 0.786; 95% CI, 0.479-1.289; P=0.340), and 28/188 patients (15%) treated with clazosentan 15 mg/h (OR, 0.474; 95% CI, 0.275-0.818; P=0.007). Poor outcome (extended Glasgow Outcome Scale score 4) occurred in 24% of patients with placebo, 25% of patients with clazosentan 5 mg/h (OR, 0.918; 95% CI, 0.546-1.544; P=0.748), and 28% of patients with clazosentan 15 mg/h (OR, 1.337; 95% CI, 0.802-2.227; P=0.266). Pulmonary complications, anemia, and hypotension were more common in patients who received clazosentan than in those who received placebo. At week 12, mortality was 6%, 4%, and 6% with placebo, clazosentan 5 mg/h, and clazosentan 15 mg/h, respectively. CONCLUSIONS: Clazosentan 15 mg/h significantly reduced postaSAH vasospasm-related morbidity/all-cause mortality; however, neither dose improved outcome (extended Glasgow Outcome Scale).

DOI: https://doi.org/10.1161/STROKEAHA.111.648980

DOI: https://doi.org/10.1161/STROKEAHA.111.648980

[Title page]

Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling

R Loch Macdonald[1] M.D., Ph.D., Randall T Higashida[2] M.D., Emanuela Keller[3] M.D., Stephan A Mayer[4] M.D., Andy Molyneux[5] M.D., Andreas Raabe[6] M.D., Peter Vajkoczy[7] M.D., Isabel Wanke[8,9] M.D., Doris Bach[10] M.Sc., Aline Frey[10] PharmD., Pegah Nowbakht[10] Ph.D., Sébastien Roux[10] M.D., Neal Kassell[11] M.D.

[1]St. Michael's Hospital University Toronto, Toronto, ON, Canada

[2]University of California, California, CA, USA

[3]University of Zürich, Zürich, Switzerland

[4]Columbia University, Columbia, DC, USA

[5]University of Oxford, Oxford, United Kingdom

[6]University of Bern, Bern, Switzerland

[7]Charite Universitaetsmedizin Berlin, Berlin, Germany

[8]University Hospital of Essen, Essen, Germany

[9]Klinik Hirslanden, Zürich, Switzerland

[10]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland

[11]University of Virginia, Charlottesville, VA, USA

Corresponding author:

R. Loch Macdonald

Head, Division of Neurosurgery

St. Michael's Hospital, University of Toronto

30 Bond Street, Toronto, Ontario, Canada, M5B 1W8

Tel: +1 416-864-5393

Fax: +1 416-864-5634

Email: macdonaldlo@smh.ca

[Title page]

Cover title: Trial of clazosentan in aSAH secured by coiling

Itemized list of tables and figures: TBD for submission

Keywords: Aneurysmal subarachnoid hemorrhage; clazosentan; CONSCIOUS-3; phase III; placebo controlled; randomized; endovascular coiling

Subject codes (http://www.ahajournals.org/site/misc/subject_codes.xhtml**):**

[13] Cerebrovascular disease/stroke

[193] Clinical studies

[50] Cerebral Aneurysm, AVM, & Subarachnoid hemorrhage

[74] Other Stroke Treatment – Medical

Current word count: 4,483

Current table/figure count: 6

Abstract

Word count: 250 (250 words maximum)

Background and purpose: Clazosentan, an endothelin receptor antagonist, has been shown to reduce vasospasm after aneurysmal subarachnoid hemorrhage (aSAH). CONSCIOUS-3 assessed whether clazosentan reduced vasospasm-related morbidity and all-cause mortality after aSAH secured by endovascular coiling.

Methods: This double-blind, placebo-controlled, phase III trial randomized patients with aSAH secured by endovascular coiling to receive intravenous clazosentan (5 or 15mg/h) or placebo for ≤14 days. The primary composite endpoint (all-cause mortality; new cerebral infarcts; delayed ischemic neurological deficit due to vasospasm; rescue therapy for vasospasm) was evaluated 6-weeks post-aSAH and reviewed centrally by a blinded critical events committee. The main secondary endpoint was the extended Glasgow Outcome Scale (GOSE; dichotomized, week 12).

Results: CONSCIOUS-3 was halted prematurely following non-significant results from CONSCIOUS-2; 577/1,470 (39%) of the planned patients were enrolled and 571 treated (placebo n=189, clazosentan 5mg/h n=194, clazosentan 15mg/h n=188). The primary endpoint occurred in 27% of placebo-treated patients, compared with 24% treated with clazosentan 5mg/h (odds ratio [OR]= 0.786, *P*=0.340), and 15% treated with clazosentan 15mg/h (OR=0.474, *P*=0.007). Poor functional outcome (GOSE score ≤4) occurred in 24% (placebo), 25% (clazosentan 5mg/h; *P*=0.748), and 28% (clazosentan 15mg/h; *P*=0.266) of patients. Pulmonary complications, anemia, and hypotension were more common in patients receiving clazosentan than placebo. At week 12, mortality rates were 6.3%, 3.6% and 6.4% with placebo, clazosentan 5 and 15mg/h, respectively.

Conclusions: Clazosentan at 15mg/h significantly reduced vasospasm-related morbidity/all-cause mortality after aSAH; the effect with clazosentan 5mg/h was not significant. Neither dose improved functional outcome (GOSE).

Clinical trial registration-URL: http://www.clinicaltrials.gov. **Unique identifier:** NCT00940095

[Note, the wording relating to clinical trial registration is a journal requirement]

Introduction

Cerebral vasospasm is the leading cause of mortality and disability following aneurysmal subarachnoid hemorrhage (aSAH).[1] Of those who survive aSAH, angiographic vasospasm accounts for approximately 50% of deaths.[2] Vasospasm also contributes to delayed ischemic neurological deficits (DIND) that occur in up to 40% of aSAH cases, and approximately half of patients with DIND develop ischemic infarctions.[3] As vasospasm after aSAH is unpredictable, common, difficult to manage, and associated with poor long-term outcomes, prevention is a highly desired management strategy; prophylactic nimodipine and hemodynamic rescue therapies are widely used, although evidence for their efficacy is limited.[2]

The pathogenesis of angiographic vasospasm includes increased levels of vasoconstrictors, such as endothelin 1.[4,5] Clazosentan is a selective endothelin receptor antagonist, which was investigated for prevention of angiographic vasospasm in patients with aSAH in the phase IIb CONSCIOUS-1 (clazosentan to overcome neurological ischemia and infarct occurring after subarachnoid hemorrhage) study.[6] In CONSCIOUS-1, clazosentan (1, 5, and 15mg/h) produced a dose-dependent reduction in moderate or severe angiographic vasospasm with a 65% relative risk reduction (RRR) with the highest dose ($p<0.0001$).

On the basis of CONSCIOUS-1, two phase III studies (CONSCIOUS-2 and CONSCIOUS-3) were designed to assess the effect of clazosentan on the incidence of cerebral vasospasm-related morbidity and all-cause mortality, and clinical outcome, in patients with aSAH and substantial subarachnoid blood who were at high risk of developing DIND. In CONSCIOUS-2, patients who had their aSAH secured by clipping received placebo or clazosentan 5mg/h; however, no effect was seen with active treatment.[7] Use of the 15mg/h clazosentan dose in CONSCIOUS-3 was based on CONSCIOUS-1 study data, where the effect of clazosentan was less with 5mg/h in aSAH secured by coiling than by clipping.[6]

CONSCIOUS-3 was initiated on 10 July 2009. The trial was halted prematurely following non-significant results from the parallel CONSCIOUS-2 clipping study,[7] and subsequent recommendations from the Data and Safety Monitoring Board (DSMB). A total of 577 patients, representing 39% of the planned 1,470 sample size, had been randomized at the time of study termination; this article reports outcomes for the 571 patients who received treatment.

Methods

This was a phase III, prospective, multicenter, international, randomized, double-blind, placebo-controlled trial (NCT00940095). Eligible patients were 18-75 years old with aSAH due to ruptured saccular aneurysm secured by endovascular coiling, with any thick clot (short axis ≥4 mm) on baseline computed tomographic (CT) scan, World Federation of Neurological Surgeons (WFNS) grades I-IV prior to coiling procedure, and able to start study drug within 56 hours of aneurysm rupture. Women of childbearing potential were included only following a negative pregnancy test. Written informed consent was obtained.

Exclusion criteria included: giant aneurysms (height or width ≥25 mm); intraventricular or intracerebral blood in the absence of subarachnoid blood; vasospasm on pre-coiling angiogram; a major complication during coiling procedure; current ruptured aneurysm previously secured (successfully or not) by clipping; missing digital subtraction angiography at the end of the coiling procedure; or several aneurysms among which the ruptured one was not identifiable with certainty and that were not all secured during the coiling procedure. In addition, intravenous nimodipine or intravenous nicardipine within 4 hours, or intravenous fasudil within 24 hours, before study drug initiation was not permitted.

After coiling, patients were randomized (1:1:1) to receive intravenous clazosentan (5 or 15mg/h) or placebo for up to 14-days post-aSAH; the investigator completed a randomization form on an interactive, independent web response system, which assigned a randomization number for each patient according to a predefined scheme. Randomization was stratified by site. The randomization code was only available to authorized individuals with no involvement in study conduct or analysis until the time of unblinding.

Sites were asked to manage patients according to guidelines developed for the study and consistent with published recommendations.[6,8] Early detection and management of lung complications were also addressed. Drugs or procedures not considered standard care were prohibited. Oral, but not intravenous, nimodipine was permitted during the study.

The study protocol was approved by local Institutional Review Boards and was completed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Assessments

Prior to the coiling procedure, all patients underwent a CT scan and catheter or CT angiography at baseline. Additional CT scans were performed 24-48 hours after the coiling procedure (12 hours for sedated patients), at discharge (unless this occurred after the 6-week visit), 6 weeks after aSAH, and in cases of worsening neurological condition (also for cerebral angiograms) or DIND (also for cerebral angiograms). For cerebral angiograms, additional angiograms were performed after coiling to document the completeness of occlusion, or if symptoms suggestive of DIND. In sedated or otherwise unevaluable patients, an angiogram was performed at day 9±2.

After treatment initiation, neurological assessments were performed every 6 hours until day 14 (irrespective of study drug duration) using the modified Glasgow Coma Scale (mGCS) and the abbreviated National Institutes of Health Stroke Scale (NIHSS).[9,10] Assessment of Glasgow Outcome Scale [extended version, GOSE][11] and modified Rankin Scale[12] were carried out at week 12 by trained centralized interviewers via a structured telephone interview.

All clinical and imaging data were reviewed by a centralized critical events committee (CEC). The CEC included an image review committee of neuroradiologists, who provided independent evaluation of CT scans and angiograms (each angiogram was reviewed by two neuroradiologists, with a third adjudicating if discrepancies occurred), and a clinical review committee (CRC) comprised of neurosurgeons and neurointensivists. The CRC made the final assessment regarding whether events were vasospasm-related and also gauged the contribution of angiographic vasospasm to poor clinical outcome (GOSE ≤4) at week 12. Individual components of the primary endpoint were evaluated by two neurosurgeons and one neurointensivist from the CRC; unanimity or consensus agreement was required.

The primary efficacy endpoint assessed angiographic vasospasm-related morbidity and all-cause mortality within 6 weeks of aSAH, as defined by at least one of the following: death; vasospasm-related cerebral infarction (where vasospasm was the primary cause or a relevant contributing factor); DIND due to vasospasm (where vasospasm was the primary cause or a relevant contributing factor) [DIND was a decrease of ≥2 mGCS points or an increase of ≥2 points on the abbreviated NIHSS lasting for ≥2 h. For patients under continuous sedation, DIND was defined as administration of valid rescue therapy, which included initiation or increase in dose of an intravenous vasopressor with or

without fluid therapy, or intra-arterial vasodilator or balloon angioplasty]; or neurological signs or symptoms, in the presence of a positive angiogram, leading to rescue therapy.

The main secondary endpoint was the GOSE, dichotomized as good [>4] or poor [≤4], at week 12. Additional secondary endpoints included occurrence of the individual components of the composite primary endpoint, and total volume of all new or worsened cerebral infarcts at week 6 post-aSAH. Planned supplementary analyses assessed the impact of subgroups (WFNS grade, clot size, age, and gender) on the primary and main secondary endpoint. Safety endpoints included death up to week 12 and treatment-emergent adverse events (AEs).

Statistical analyses

Assuming a RRR of 30% (odds ratio [OR]=0.603) with at least one dose of clazosentan (5 or 15mg/h) and a placebo event rate of 35%, it was calculated that with a total sample size of 1,470, a two-group continuity-corrected Chi-Square test had approximately 90% power to reject the null hypothesis (comparison-wise, two-sided, error rate of 2.5%).

This trial was halted prematurely after non-significant results from the parallel CONSCIOUS-2 clipping study became apparent,[7] and subsequent recommendations from the DSMB; as such, planned confirmatory analyses were not performed and formal testing of the global null hypothesis was not carried out. Treatment effect of the two clazosentan doses was tested in an exploratory manner using logistic regression adjusting for WFNS grade (≤II, >II) and described using OR with the corresponding 95% confidence intervals (CIs). Dichotomized GOSE was analyzed using the same statistical methods as for the primary endpoint. In the case of a missing assessment for the morbidity component of the primary endpoint, or missing information on the vital status, the worst case (i.e., presence of vasospasm-related morbidity and mortality) was assumed. For GOSE, if no score was available, a score of 5 was assigned when there was no clinical evidence of prior neurological impairment, and a score of 3 given in any other situation when a patient was alive at week 12. Baseline demographics were analyzed using descriptive statistics; all values are mean and standard deviation (SD), or percent.

Efficacy analyses were based on the full analysis set, defined as all treated patients (i.e., all those randomized who started infusion). Analysis of the primary outcome was also performed on the per-

protocol set, encompassing all patients without major protocol violations. Patients exposed to treatment, with at least one post-baseline safety measurement, were included in the safety dataset.

Additional information on the rationale, study design and methodology has been published.[13]

Results

Baseline characteristics

CONSCIOUS-3 was conducted between 10 July 2009 and 26 January 2011 (last patient, last visit) at 106 centers in 27 countries; 577 of 1,470 patients (39% of the planned sample size) had been randomized at the time of study termination, and 571 (placebo n=189, clazosentan 5mg/h n=194, clazosentan 15mg/h n=188) had received treatment. Participant flow is shown in Figure 1. Adverse events were the most common reason for discontinuation of study drug in all arms; administrative/other reasons included stopping drug by mistake, early hospital discharge, and other technical/logistical reasons. Demographic and clinical characteristics were similar across all randomized groups at baseline (Table 1) and were characteristic of patients with aSAH.

Patients received study treatment for a mean (SD) of 12 (2), 12 (3), and 12 (3) days in the placebo, clazosentan 5mg/h and 15mg/h groups, respectively, with treatment commencing 18 (12), 20 (12), and 18 (12) hours, respectively, after aneurysm coiling. Oral nimodipine was administered concomitantly to 94% (placebo), 95% (clazosentan 5mg/h), and 95% (clazosentan 15mg/h) of patients.

Data for the primary endpoint were substituted for one patient with missing data in the clazosentan 5mg/h group. For the GOSE secondary endpoint, four patients had data substituted in the placebo group (two with GOSE score 3; two with GOSE score 5), six patients had data substituted in the clazosentan 5mg/h group (six with GOSE score 3; none with GOSE score 5), and three patients had data substituted in the clazosentan 15mg/h group (two with GOSE score 3; one with GOSE score 5).

Efficacy

Vasospasm-related morbidity and all-cause mortality occurred in the all-treated population in 26% of patients in the placebo group compared with 24% and 15% in the 5 and 15mg/h clazosentan groups, respectively; a significant improvement was seen with 15mg/h clazosentan (RRR=44%; OR=0.474,

95% CI 28-82%; *P*=0.007), but not with 5mg/h (RRR=8%; OR=0.786, 95% CI 48-129%; *P*=0.340) (Figure 2a). In the per-protocol population, the event rates were 28% (placebo), 26% (clazosentan 5mg/h; RRR=8%; OR=0.768, 95% CI 46-129%; *P*=0.321), and 15% (clazosentan 15mg/h; RRR=48%; OR=0.441, 95% CI 24-80%; *P*=0.007) of patients. Event rates in the all-treated population for each individual component of the composite endpoint are shown in Figure 2b; a higher proportion of patients required rescue therapy in the placebo group (21%) compared with clazosentan 5mg/h (15%) and 15mg/h (7%).

Poor functional outcome (GOSE score ≤4; endpoint substituted) occurred in 24% of patients in the all-treated placebo group compared with 25% (RRR=4%; OR=0.918, 95% CI 55-154%; *P*=0.748) and 28% (RRR=14%; OR=1.337, 95% CI 80-223%; *P*=0.266) in the clazosentan 5 and 15mg/h groups, respectively.

In the placebo group, the CEC-confirmed new cerebral infarct mean total volume at week 6 post-aSAH was 50.40 cm^3 compared with the clazosentan 5mg/h and 15mg/h groups (40.74 cm^3 and 59.03 cm^3, respectively).

Results from planned subgroup analyses of vasospasm-related morbidity and all cause mortality, and occurrence of poor GOSE outcome, according to sex, age, baseline clot size, and WFNS grade at baseline are shown in Figures 3 and 4.

Safety and tolerability

During the study, 91%, 86%, and 92% of patients receiving placebo, clazosentan 5 and 15mg/h, respectively, experienced ≥1 AE. The most commonly-reported AEs were pyrexia (23%, 22%, and 26%), constipation (21%, 22%, and 22%), and cerebrovascular spasm (32%, 22%, and 14%) in the placebo, clazosentan 5 and 15mg/h groups, respectively. Severe AE incidence was 25% (placebo) 28% (clazosentan 5mg/h), and 29% (clazosentan 15mg/h); rates of AEs considered by the investigator to be related to treatment was 24%, 34%, and 37%, respectively. Incidence of AEs of specific interest is shown in Table 2.

Of treated patients, 6% (placebo), 4% (clazosentan 5mg/h), and 6% (clazosentan 15mg/h) died within 12 weeks of aSAH; causes of death reported for >1% of patients in any group were cerebral infarction (2%, <1%, and 3%), cerebrovascular spasm (2%, <1%, and <1%), and brain edema (2%, <1%, and <1%), respectively.

Discussion

This randomized, double-blind, placebo-controlled, phase III trial investigated outcomes with clazosentan 5 or 15mg/h administered for up to 14 days in patients with aSAH secured by endovascular coiling. The trial was halted early due to non-significant findings with clazosentan 5mg/h in the parallel CONSCIOUS-2 clipping study.[7] For the lower dose, data from the present study support findings from CONSCIOUS-2, i.e. clazosentan 5mg/h had no significant effect on vasospasm-related morbidity or all-cause mortality 6-weeks post-aSAH (composite primary endpoint) or functional outcome. Nonetheless, the main objective of demonstrating that at least one dose (5 or 15mg/h) of clazosentan reduces vasospasm-related morbidity or all-cause mortality within 6-weeks post-aSAH was met: a statistically significant treatment effect of clazosentan 15mg/h was observed for the primary endpoint. The reduction in the primary endpoint event rate did not translate into improved functional outcomes at week 12, as measured by GOSE. However, the effect of 15mg/h clazosentan on vasospasm-related morbidity events provides further support for a dose-related effect on the occurrence of cerebrovascular spasm post-aSAH as observed in the phase IIb CONSCIOUS-1 study where the 15mg/h clazosentan dose significantly reduced mortality and vasospasm-related morbidity.[6]

Some explanations for the lack of effect of the 5mg/h clazosentan dose have been documented.[7] Reasons include the possibility that the tolerability profile of the drug negated therapeutic benefit or that interaction with oral nimodipine contributed to AEs. Rescue therapy may provide a positive effect on outcome that obscures the benefit of clazosentan. Other factors may also contribute to poor outcome that are not treated by clazosentan. Interestingly, the causes of death/AEs in the placebo group related to vasospasm were higher than in the clazosentan groups, while non-vasospasm related causes were higher in the clazosentan groups. Additionally, the GOSE may not detect meaningful improvements in outcome. Central assessment of the primary endpoint, which ensured the specificity was high, could have decreased the sensitivity by excluding questionable events.

In the present study, which investigated 15mg/h clazosentan as well as 5mg/h, the higher dose reduced vasospasm-related morbidity or all-cause mortality within 6-weeks post-aSAH, but did not improve functional outcomes. If it is assumed that rescue therapy prevents the ischemic consequences of vasospasm on long term clinical outcome, the three-fold more frequent use of rescue therapy in the 15mg/h group compared with the placebo arm could have accounted for the

lack of treatment effect observed on GOSE. Due to the early stopping of this trial, the planned number of patients was not enrolled, therefore, it cannot be ruled out that low statistical power may explain the lack of effect observed with 5mg/h clazosentan. Preplanned subgroup analyses of the primary endpoint and dichotomized GOSE scores did not reveal an obvious explanation for the outcome of this study. For future trials, investigating different durations of clazosentan administration could be considered.[14,15]

A higher proportion of patients receiving clazosentan (5 mg/h and 15 mg/h) prematurely discontinued treatment compared with the placebo group; the main reason for discontinuation from study drug was AEs. The AEs (lung complications, hypotension, and anemia) experienced by the patients in this study were consistent with those observed in CONSCIOUS-1 and CONSCIOUS-2, suggesting no new safety concerns. An equal proportion of patients in the clazosentan 15mg/h and placebo groups died during the study, with cerebral infarction the most frequently-reported primary cause of death in these groups.

Summary

Clazosentan at 15mg/h reduced cerebral vasospasm-related morbidity and all-cause mortality; however, the effect with clazosentan 5mg/h was not significant. Neither dose improved functional outcome as measured by GOSE, possibly due to greater use of rescue therapy in the placebo group. Compared with placebo, pulmonary complications, anemia, and hypotension were more common in patients receiving clazosentan, particularly with the higher dose; however, no new safety concerns were observed.

Acknowledgements

The authors thank Kim Croskery and Catherine Jones (Watermeadow Medical, Witney, UK) for their writing and editorial assistance, supported by Actelion Pharmaceuticals.

Sources of funding

This study was funded by Actelion Pharmaceuticals Ltd.

Disclosures

RLM receives grant support from Actelion Pharmaceuticals Ltd, and is a stockholder of Edge Therapeutics. RLM, RTH, EK, SAM, AMo, AR, PV, IW, and NK are consultants for Actelion Pharmaceuticals Ltd. EK has been on speakers' bureaus for Zoll Medical, received research grants from Swiss National Science Foundation, and is a stockholder in NeMoDevices. AMo has been a consultant for Micrus Endovascular, and receives grant support from the Medical Research Council UK and Cerecyte Coil Trial Micrus Inc. DB, AF, PN, and SR are employees and stockholders of Actelion Pharmaceuticals Ltd.

References

(1) Crowley RW, Medel R, Kassell NF, Dumont AS. New insights into the causes and therapy of cerebral vasospasm following subarachnoid hemorrhage. Drug Discov Today. 2008;13:254-260.

(2) Bederson JB, Connolly ES, Jr., Batjer HH, Dacey RG, Dion JE, Diringer MN et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke. 2009;40:994-1025.

(3) de Oliveira JG, Beck J, Ulrich C, Rathert J, Raabe A, Seifert V. Comparison between clipping and coiling on the incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Neurosurg Rev. 2007;30:22-30.

(4) Kolias AG, Sen J, Belli A. Pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: putative mechanisms and novel approaches. J Neurosci Res. 2009;87:1-11.

(5) Kramer A, Fletcher J. Do endothelin-receptor antagonists prevent delayed neurological deficits and poor outcomes after aneurysmal subarachnoid hemorrhage?: a meta-analysis. Stroke. 2009;40:3403-3406.

(6) Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. Stroke. 2008;39:3015-3021.

(7) Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage

undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). Lancet Neurol. 2011;10:618-625.

(8) Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC, Jr., Brott T et al. Recommendations for the management of patients with unruptured intracranial aneurysms: A Statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke. 2000;31:2742-2750.

(9) Schlegel D, Kolb SJ, Luciano JM, Tovar JM, Cucchiara BL, Liebeskind DS et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke. 2003;34:134-137.

(10) Lyden P, Lu M, Jackson C, Marler J, Kothari R, Brott T et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. Stroke. 1999;30:2347-2354.

(11) Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma. 1998;15:573-585.

(12) Quinn TJ, Dawson J, Walters MR, Lees KR. Functional outcome measures in contemporary stroke trials. Int J Stroke. 2009;4:200-205.

(13) Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A et al. Preventing vasospasm improves outcome after aneurysmal subarachnoid hemorrhage: rationale and design of CONSCIOUS-2 and CONSCIOUS-3 trials. Neurocrit Care. 2010;13:416-424.

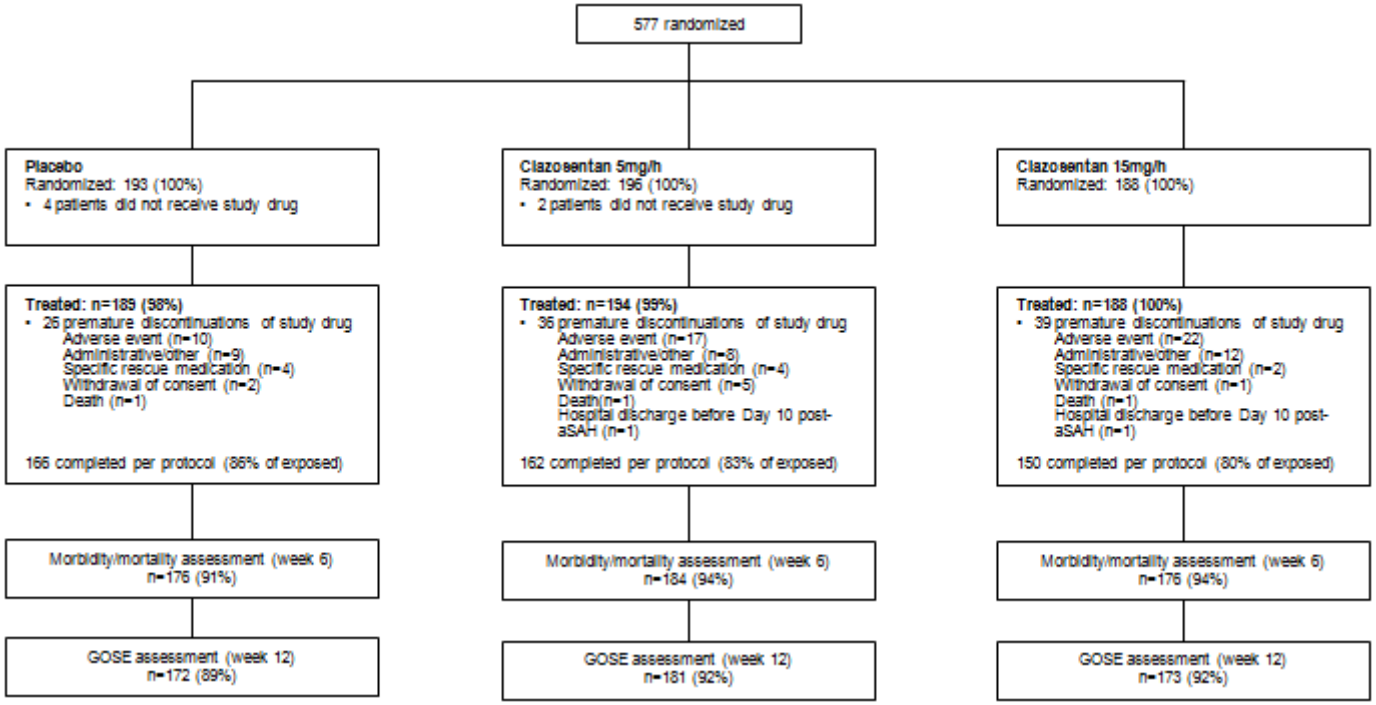
(14) Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A et al. Clazosentan for patients with subarachnoid haemorrhage: lessons learned - Authors' reply. Lancet Neurol. 2011;10:871-872.

(15) Wong GK, Poon WS. Clazosentan for patients with subarachnoid haemorrhage: lessons learned. Lancet Neurol. 2011;10:871.

Figures

[Note that the figures presented below will be redrawn according to the journal style and author preferences prior to manuscript submission]

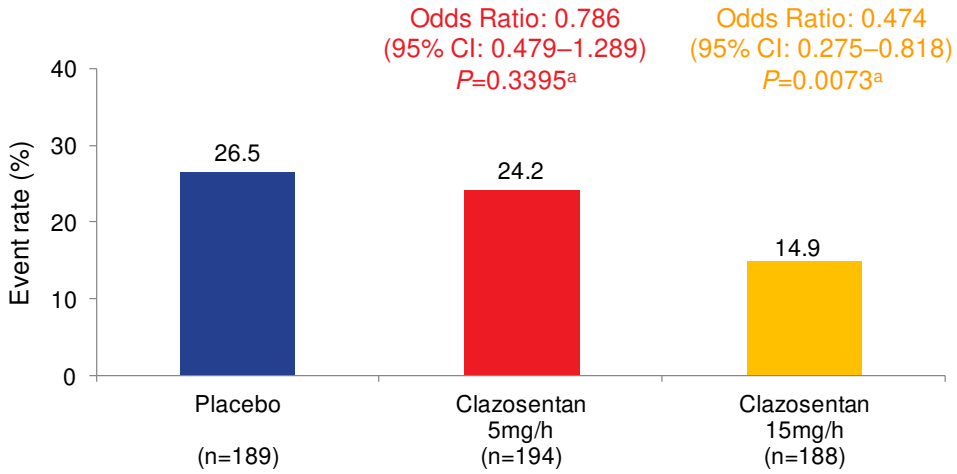
Figure 1: Participant flow.



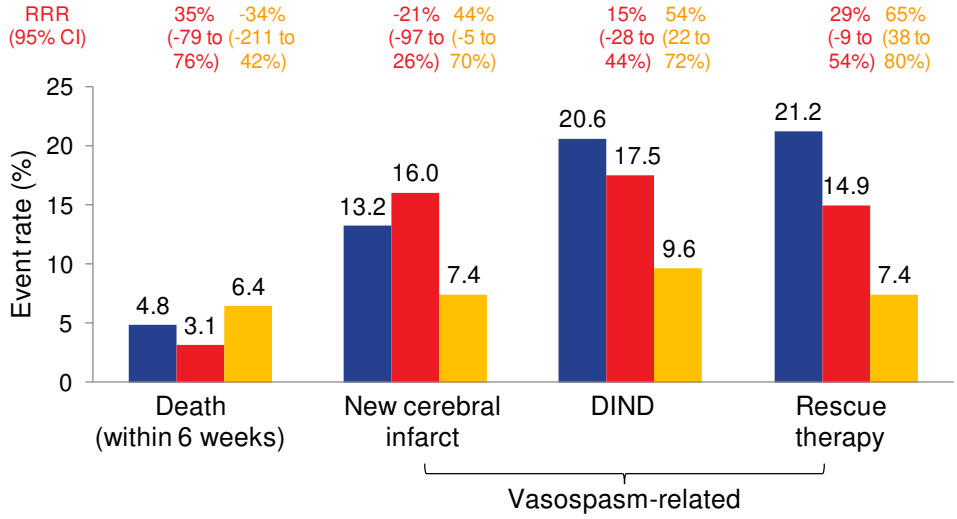
aSAH: aneurysmal subarachnoid hemorrhage; GOSE: extended Glasgow Outcome Scale; WFNS: World Federation of Neurological Surgeons.

Figure 2: Event rate (%) for: a) all cause mortality and vasospasm-related morbidity at 6 weeks (all-treated, endpoint substituted); and b) each of the individual components of the primary composite endpoint (all-treated, endpoint substituted; planned analysis, secondary endpoint).

a)



b)

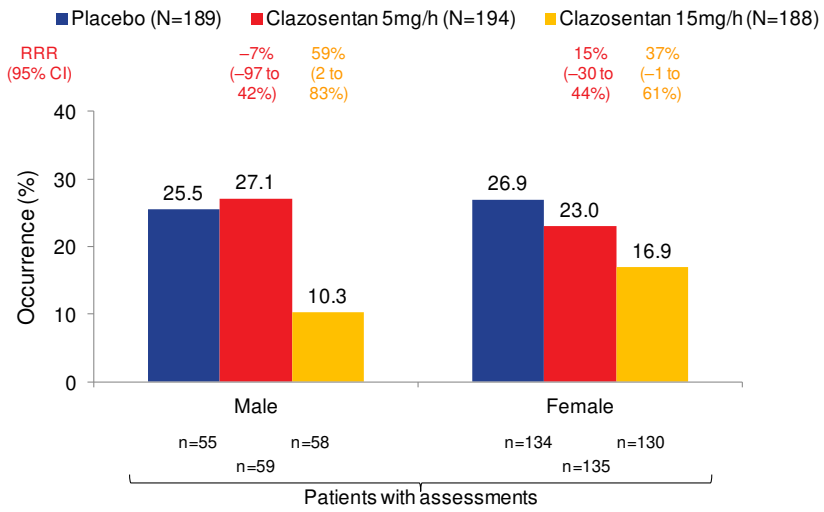


[a]Adjusted by WFNS, logistic regression

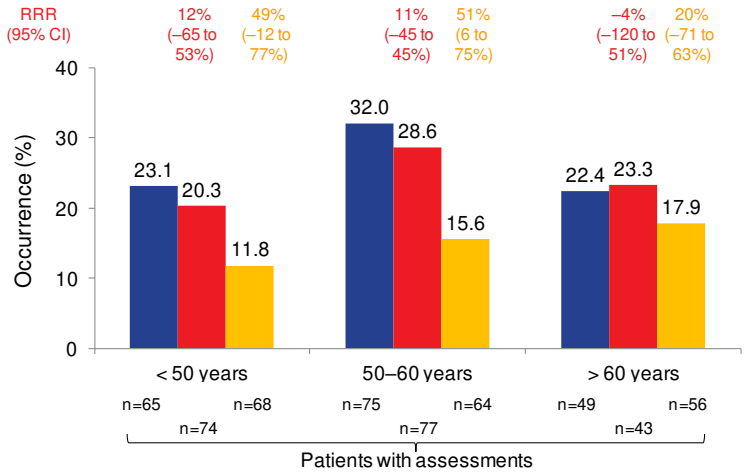
RRR: relative risk reduction; CI: confidence interval; DIND: delayed ischemic neurological deficit

Figure 3. Effect of a) sex, b) age, c) baseline clot size, and d) WFNS grade at baseline on occurrence (%) of vasospasm-related morbidity and all cause mortality (all-treated; endpoint substituted).

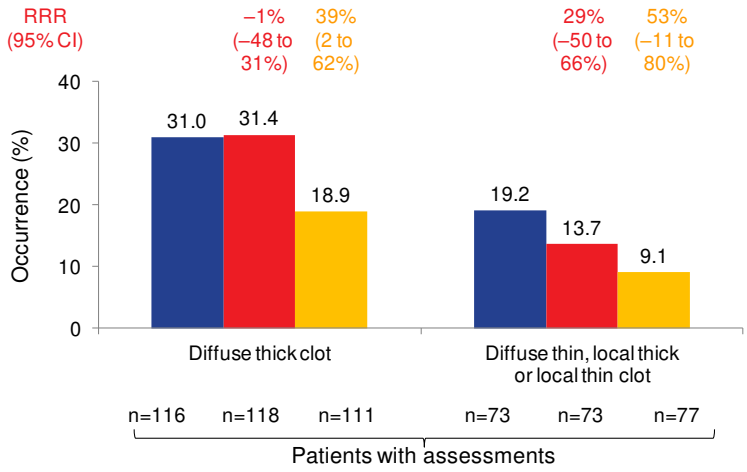
a)



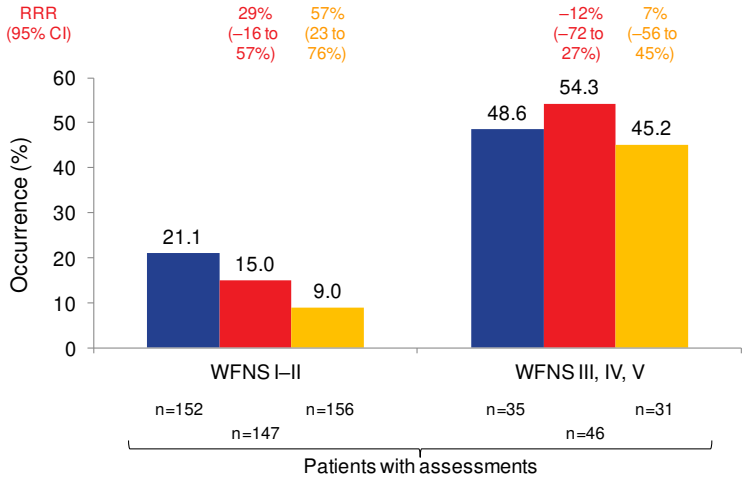
b)



c)



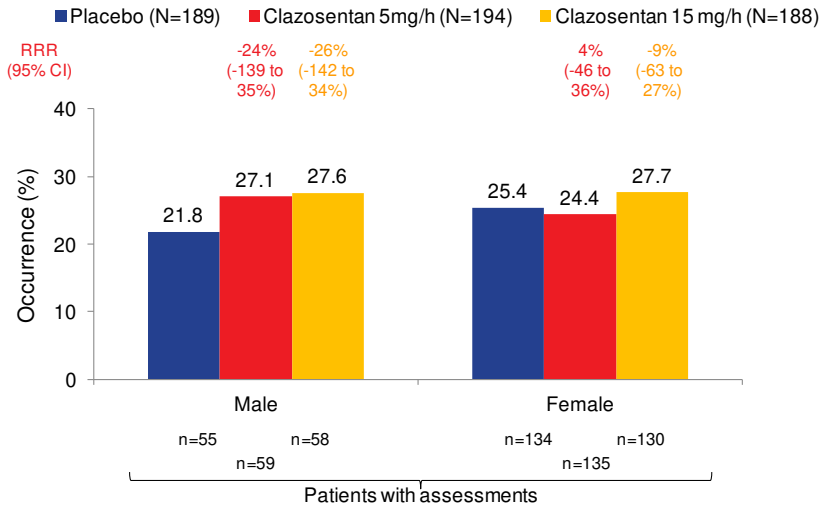
d)



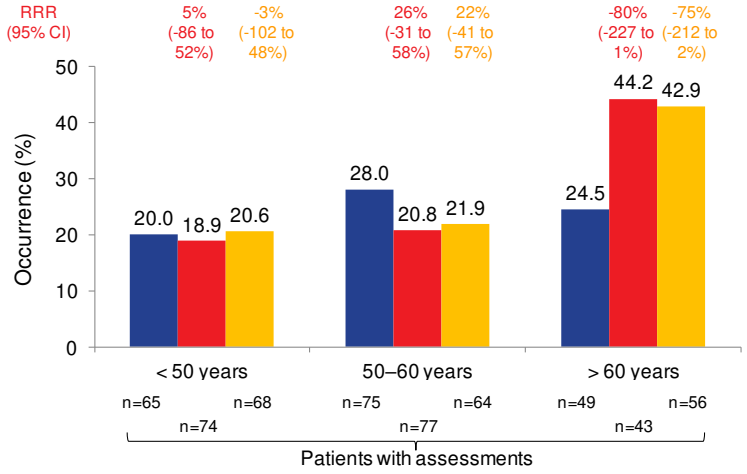
WFNS: World Federation of Neurological Surgeons

Figure 4. Effect of a) sex, b) age, c) baseline clot size, and d) WFNS grade at baseline on occurrence (%) of poor GOSE outcome (all-treated; endpoint substituted).

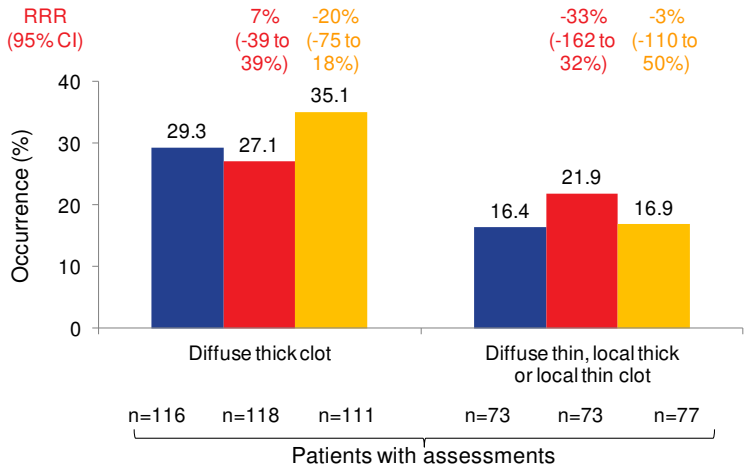
a)



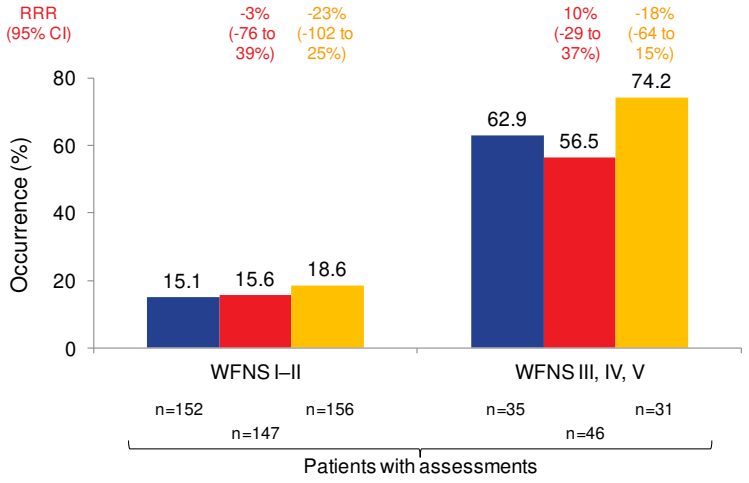
b)



c)



d)



WFNS: World Federation of Neurological Surgeons

Tables

Table 1: Baseline demographic and disease characteristics (all-treated).

Characteristic	Placebo n=189	Clazosentan 5mg/h n=194	Clazosentan 15mg/h n=188	Total n=571
Male	55 (29)	59 (30)	58 (31)	172 (30)
Mean (SD) age, years	54 (11)	52 (11)	53.6 (11)	53.1 (11)
Age range, years	23-75	23-75	19-76	19-76
WFNS admission grade				
Grade I	96 (51)	99 (51)	103 (55)	298 (53)
Grade II	56 (30)	48 (25)	53 (28)	157 (28)
Grade III	6 (3)	5 (3)	3 (2)	14 (3)
Grade IV	24 (13)	37 (19)	26 (14)	87 (15)
Grade V	5 (3)	4 (2)	2 (1)	11 (2)
Motor deficit present at admission	19 (10)	21 (11)	18 (10)	58 (10)
Number of aneurysms secured (ruptured and unruptured)				
1	183 (97)	183 (94)	177 (94)	543 (95)
2	6 (3)	10 (5)	10 (5)	26 (5)
>2	0	1 (<1)	1 (<1)	2 (<1)
Size of clipped ruptured aneurysm				
≤15 mm	183 (98)	193 (100)	181 (97)	557 (98)
>15 mm	5 (3)	1 (<1)	6 (3)	12 (2)
Key locations of ruptured aneurysms				
Supraclinoid ICA	19 (10)	22 (11)	31 (17)	72 (13)
MCA	16 (9)	19 (10)	23 (12)	58 (10)
ACA	10 (5)	21 (11)	13 (7)	44 (8)
ACoA	74 (39)	62 (32)	62 (33)	198 (35)
PCoA	31 (16)	39 (20)	35 (19)	105 (18)
Distal VA	11 (6)	5 (3)	8 (4)	24 (4)

Characteristic	Placebo n=189	Clazosentan 5mg/h n=194	Clazosentan 15mg/h n=188	Total n=571
Basilar artery	22 (12)	22 (11)	15 (8)	59 (10)
Clot size at baseline				
Diffuse thick	116 (61)	118 (61)	111 (59)	345 (61)
Local thick	58 (31)	54 (28)	56 (30)	168 (30)
Diffuse thin	12 (6)	17 (9)	17 (9)	46 (8)
Local thin	3 (2)	2 (1)	4 (2)	9 (2)
Unable to assess	0	2 (1)	0	2 (<1)

Values are n (%) unless otherwise stated

ACA: anterior cerebral artery; ACoA: anterior communicating aneurysm; ICA: internal carotid artery; MCA: middle cerebral artery; PCoA: posterior communicating artery; WFNS: World Federation of Neurological Surgeons.

Table 2. Adverse events of specific interest occurring up to 1 day after study drug discontinuation and up to week 6 post aSAH (safety population).

Grouping of MedDRA terms; patients with ≥1 AE n (%)	**Placebo n=189**	**Clazosentan 5 mg/h n=194**	**Clazosentan 15 mg/h n=188**
Lung complications	40 (21)	70 (36)	70 (37)
Lung complications related to pulmonary edema	16 (9)	37 (19)	32 (17)
Hypotension	13 (7)	21 (11)	30 (16)
Hepatobiliary events	35 (19)	39 (20)	28 (15)
Anemia	18 (10)	25 (13)	24 (13)
Rhythm/conduction disorders	23 (12)	16 (8)	20 (11)
Cerebral hemorrhage	5 (3	7 (4	7 (4)
Cardiac ischemic events	3 (2)	8 (4)	6 (3)
Eye disorders	0	0	6 (3)

MedDRA, medical dictionary for regulatory activities